DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 30 December 2008.

Claim Status

Claims 1-3, 5-7, 18 and 20-24 are pending. However, claims 18 and 20-24 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1, 5, 7 are amended. Claims 4, 8-17, 19 and 25-28 are canceled. Claims 1-3 and 5-7 are under current examination.

Priority

This application claims benefit as a PCT/EP04/53604 (filed 12/20/2004) which claims benefit of 60/541,771 (filed 02/05/2004). This application claims benefit from foreign application EPO 03029367.4 (filed 12/19/2003).

The instant application has been granted the benefit date, 19 December 2003, from foreign application EPO 03029367.4.

Information Disclosure Statement

The applicant states that on October 26, 2006, copies of the cited references were submitted with the PTO-1449 Information Disclosure Statement (IDS). The applicant correctly notes that on the copy of the IDS filed with the action of 6/30/2008, the examiner had lined through all the references indicated on the PTO-1449 (filed 10/26/2006). The examiner was unable to find a copy of the cited references. Therefore, they were not considered. If the examiner wishes the references to be considered, they must be submitted. Accordingly, examiner has considered the Information Disclosure Statement, but none of the references listed thereon were considered.

Specification

The objection to the specification is hereby withdrawn. The applicant has submitted amendments to the specification which have replaced instances of the phrase "Seq.Id.No" with "SEQ ID NO:." The objectionable matter has been corrected.

Claim Objections

The objections to claims 1, 4, and 7 are withdrawn in response to the claim amendments submitted by the applicant.

RESPONSE TO ARGUMENTS

Claim Rejections - 35 USC § 112

The rejection of claim 4 under 35 USC 112, 2nd paragraph is withdrawn in response to the applicants claim amendments.

The applicant has cancelled the claim 4. Therefore, the rejection is moot.

Therefore, the examiner hereby withdraws the rejection of claim 4 under 35 USC 112, 2nd paragraph.

Claim Rejections - 35 USC § 103

The rejection of claims 1-3 and 5-6 under 35 U.S.C. 103(a) as being unpatentable over Roth et al. (Cellular and Molecular Life Sciences. 1999; 56: 481-506) is withdrawn in response to the applicants claim amendments.

The applicant has cancelled claim 4 and incorporated the limitations into claim 1. Newly amended claim 1 encompasses oligonucleotides comprising at least one of the sequences, SEQ ID NO:1-78. Roth et al. do not teach these sequences. Therefore, the rejection is moot.

Therefore, the examiner hereby withdraws the rejection of claims 1-3 and 5-6 under 35 U.S.C. 103(a) as being unpatentable over Roth et al. (Cellular and Molecular Life Sciences. 1999; 56: 481-506).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 5-7 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Roth et al. (Cellular and Molecular Life Sciences. 1999; 56: 481-506) in view of Jachimczak et al. (Int. J. Cancer. 1996; 65: 332-337) for the reasons of record and the comments below.

The applicant's arguments and claim amendments have been fully considered but are persuasive. The applicant has amended claim 1 to incorporate limitations from cancelled claim 4 into claim 1; these limitations encompasses oligonucleotides comprising at least one of the sequences, SEQ ID NO:1-78. These limitations were discussed the last Office Action' obviousness rejection over Roth in view of Jachimczak

The applicant presents a theory that the antisense TGF-beta of Jachimczak, which is identical to instantly claimed SEQ ID NO:1, that "the skilled person would have inferred that the antisense TGF beta described by Jachimczak et al .had already been tested in immunochemotherapies without success." (Remarks, page 20, parag.1). The applicant also refers to the composition of Roth in view of Jachimczak as "inoperative." (Remarks, page 20, parag.2). The examiner finds this argument unpersuasive, because the rejection is an obviousness rejection and not an enablement rejection. Furthermore, Roth proposes pharmaceutical compositions comprising a genus of TGF-beta antisense nucleic acids and Temozolomide. Jachimczak describes a particular species of TGF-beta antisense nucleic acids identical to instantly claimed SEQ ID NO:1. Whether nor not this combination would be therapeutic, is not under discussion. The pharmaceutical composition is suggested by the prior art. A product is being claims and not a method.

The applicant further argues that the cited art teaches away from the claimed pharmaceutical composition. The examiner does not find this argument persuasive, because Roth et al. teach combination therapies and further teach the individual components of such combination therapies: Temozolomide and the genus of TGF-beta

antisense nucleic acids. Jachimczak describes a particular species of TGF-beta antisense nucleic acids identical to instantly claimed SEQ ID NO:1. Therefore, Roth in view of Jachimczak suggest a pharmaceutical composition comprising Temozolomide and the particular species of TGF-beta antisense oligonucleotides, CGATAGTCTTGCAG, which is identical to instantly claimed SEQ ID NO:1. The applicant suggests that the cited references teach away because "the product would not have the property sought by the applicant." (Remark, page 20, 2nd parag.). Any property sought by the applicant would be intrinsic to the constituent components of the claimed composition. Since the cited art suggests the constituent molecules of the claimed composition, the examiner concludes that the claim limitations have been met.

Therefore, the applicant's arguments are unpersuasive.

Accordingly, the examiner hereby maintains the rejection of claims 1-3 and 5-7 under 35 U.S.C. 103(a) as being unpatentable over Roth et al. in view of Jachimczak et al.

The examiner reiterates the pending rejection below:

Claims 1-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roth et al. (Cellular and Molecular Life Sciences. 1999; 56: 481-506) in view of Jachimczak et al. (Int. J. Cancer. 1996; 65: 332-337).

Claim 1 is directed to a pharmaceutical composition comprising at least one TGF-beta antagonist, selected from the group consisting of - oligonucleotides hybridizing with an area of the messenger RNA (mRNA) and/or DNA encoding TGF-beta, wherein the oligonucleotide comprises at least one of the sequences of SEQ ID

NO:1-78, - TGF-beta receptors and/or parts of them binding TGF-beta, - proteins, except antibodies, inhibiting TGF-beta - peptides of less than 100 kDa inhibiting TGF-beta - peptides being parts of TGF-beta and at least one substance inhibiting cell proliferation and/or inducing cell death selected from the group consisting of temozolomide, nitrosoureas, Vinca alkaloids, antagonists of the purine and pyrimidine bases, cytostatic active antibiotics, caphthotecine derivatives, anti-androgens, anti-estrogens, anti-progesterones and analogs of gonadotropin releasing-hormone. Roth et al. teach "great efforts are being made to enhance antitumoral efficacy by combining various cytotoxic agents, by novel routes of drug administration, or by combining anticancer drugs and immune modulators." (page 481, abstract). Roth et al. teach "experimental drugs for the treatment of malignant gliomas…Temozolomide" (page 486, Table 2). Roth et al. teach "categories of immunotherapy for malignant glioma…inhibition of immunosuppressive factors, e.g, TGF-β by antisense TGF-β" (page 486, Table 3). Jachimczak et al. teach an antisense oligonucleotide against TGF-β1 with the sequence CGATAGTCTTGCAG. The sequence taught by Jachimczak et al. is 100% identical to SEQ ID NO:1 of the instant application. Jachimczak et al. teach that such oligonucleotides can be used to inhibit expression of the target protein.

Claim 2 is directed to the pharmaceutical composition of claim 1, wherein both agents mixed together. Roth et al. teach combination therapies which are simultaneously administered.

Claim 3 is directed to the pharmaceutical composition of claim 1, wherein both agents are separate. Roth et al. teach combination therapies in which it is not desirable

for simultaneously administration. Roth et al. also teach strategies which are based on alternative routes of drug administration.

Claim 5 is directed to the pharmaceutical composition according to claim 4 wherein at least one nucleotide of the oligonucleotide is modified at the sugar moiety, the base and/or the internucleotide linkage. Claim 6 is directed to the pharmaceutical composition according to claim 5 wherein at least one modified internucleotide linkage is a phosphorothioate linkage. Jachimczak et al. teach employing phosphorothioate antisense oligodeoxynucleotides…specifically targeted against the coding sequences of TGF-β1 mRNA" (page 332, abstract).

Claim 7 is directed to the pharmaceutical composition according to claim 1 wherein - the nitrosourea is selected from the group of ACNU, BCNU and CCNU, - the Vinca-alkaloid is selected from. the group of vinblastine, vincristine, vindesine, - the antagonist of the purine and pyrimidine bases is selected from the group of 5-fluorouracile, 5-fluorodeoxiuridine, cytarabine and gemcitabine, - the cytostatic antibiotic is selected from the group of doxorubicine and liposomal PEGylated doxorubicin, - the camphthotecine derivative is selected from the group of irinotecane and topotecane, - the anti estrogenes are selected from the group of tamoxifen, exemestane, anastrozole and fluvestrant, - the antiandrogens are selected from the group of flutamide and bicalutamide, - the antiprogesterons are selected from the group of mifepriston - the analogs of gonadotropin releasing horrnone are selected from the group of leuprolide and gosereline. Roth et al. teach numerous members of the Markush group recited in claim 7, including BCNU, vincristine, 5-FU and tamoxifen.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the phosphorothioate antisense oligonucleotide having the sequence CGATAGTCTTGCAG in a pharmaceutical composition comprising a combination of antisense TGF-beta oligonucleotides with at least one substance inhibiting cell proliferation and/or inducing cell death in a pharmaceutical composition.

The person of ordinary skill in the art would have been motivated to make those modifications because Jachimczak et al. teach phosphorothioate antisense oligonucleotide have enhanced stability (page 332, col.2, parag.1) and CGATAGTCTTGCAG inhibits cell proliferation in gliomas (abstract)

The skilled artisan would have had a reasonable expectation of success in making a pharmaceutical composition because these active ingredients are known in the art.

Therefore the pharmaceutical composition as taught by Roth et al. in view of Jachimczak et al. would have been *prima facie* obvious over the pharmaceutical composition of the instant application.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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